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14. ABSTRACT

PTSD and related anxiety disorders are a major health problem for veterans, as well as the general population. There is compelling experimental support for the proposition that elevated NA release in the brain is a major contributing factor in PTSD. This elevation in norepinephrine is thought to promote arousal as well as the persistence and enhanced retrieval of traumatic memories – core phenomena in PTSD. The principal source of norepinephrine in forebrain and amygdalar circuits is the locus ceruleus (LC). In spite of its centrality to theories of the neural mechanisms underlying PTSD, relatively little is known about the factors governing its activity and how these change in PTSD. The central hypothesis of this proposal is that the intrinsic and extrinsic (synaptic) properties of LC neurons are remodeled in PTSD, and this remodeling plays a major role in triggering the pathological changes in forebrain circuits mediating symptoms in the disorder. The studies to be conducted will test this core hypothesis in two animal model of PTSD, filling key gaps in our understanding of the mechanisms governing PTSD. The core hypothesis is broken down into three specific aims, each of which has a guiding, working hypothesis. The studies outlined in the first specific aim will test the hypothesis that the induction of PTSD-like state in mice will result in an elevation of autonomous (intrinsically generated) spiking in LC neurons. The studies outlined for the second specific aim will test the hypothesis that the induction of PTSD-like state in mice will result in strengthening of synaptic connections of LC neurons that arise from the cerebral cortex and amygdala, creating a means by which fear-evoking stimuli lead to an abnormal elevation of LC activity. Our lab has a well-developed expertise in the characterization of synaptic connections using both conventional electrical and optogenetic approaches. The studies outlined for the third specific aim will test the hypothesis that activity-dependent forms of plasticity will shape the synaptic connections of LC neurons, providing a means of altering the responsiveness of LC neurons to fear-evoking environmental stimuli. These studies will focus on the mechanisms governing the induction of long-term depression (LTD) and long-term potentiation (LTP).

15. SUBJECT TERMS
None provided

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1. INTRODUCTION:

Anxiety disorders affect approximately thirty percent of men and women who have spent time in war zones. In the larger general population, the lifetime prevalence of anxiety disorders is similar – making anxiety disorders a significant health and economic burden to society. One of the most common anxiety disorders ins post-traumatic stress disorder (PTSD); PTSD affects about one quarter of people exposed to traumatic events, such as accidents, military combat, and sexual abuse (*1*). PTSD symptoms include hyperarousal, sleep disturbances, and avoidance, but it remains unclear the cellular mechanisms underlying PTSD. Brain regions such as the amygdala and the medial prefrontal cortex (mPFC) have been shown to be involved in the expression and extinction of fear memories (*2*). In addition, there is growing evidence that release of norepinephrine from locus coeruleus (LC) neurons play an important role in PTSD (*3*, *4*), modulating the activity of amygdalar and mPFC neurons. However, the cellular mechanisms underlying the control of LC neurons during PTSD are not well understood. We hypothesize that increased anxiety and fear responses in PTSD are associated with long-lasting adaptations of intrinsic properties and afferent inputs that control LC neurons. The results from this research plan could help elucidate therapeutic strategies for PTSD patients.

2. KEYWORDS:

Post-traumatic stress disorder, locus coeruleus, central nucleus of the amygdala, prefrontal cortex, optogenetics, channelrhodopsin-2, fear conditioning, pacemaking, calcium, synaptic plasticity, corticotropin-releasing factor (CRF), endoplasmic reticulum, mitochondria, calcium-induced calcium release.

3. OVERALL PROJECT SUMMARY:

Specific Aim 1: To characterize changes in intrinsic physiological properties of locus ceruleus (LC) neurons in two mouse models of PTSD.

LC neurons release noradrenaline (NA) in forebrain regions implicated in PTSD (*5*). This release is dependent upon action potentials or spikes. LC neurons display two types of spiking activity modes: tonic and phasic (*6*). Initially, our efforts to understand PTSD-related adaptations in LC neurons have been focused on the characterizing the tonic mode. We discovered that this mode of spiking is autonomously generated; that is, it is independent of synaptic input. Whole-cell current clamp recordings from LC neurons revealed tonic, pacemaking activity was accompanied by an underlying membrane potential oscillation that was sensitive to the dihydropyridine isradipine, a well-known antagonist of L-type calcium channels. Using two-photon laser scanning microscopy (2PLSM) with Ca^{2+} dyes in *ex vivo* brain slices (*7*), we have found that this dihydropyridine sensitive oscillation led to pronounced fluctuations in intracellular Ca^{2+} concentration. Although prominent, opening of these channels was not necessary to sustain normal pacemaking at rest. However, these channels help support LC spiking during periods of sustained stress, like that encountered in combat situations. To demonstrate this point, we challenged LC neurons with high potassium to depolarize the cells and increase spike rate. With normally functioning L-type Ca^{2+} channels, LC neurons were able to sustain spiking for as long as we could maintain the recording (>30 minutes).

In contrast, antagonism of L-type channels diminished the capacity of LC neurons to sustain this spiking, leading to a complete cessation of spiking after only 5-10 minutes.

Another distinctive feature of LC neurons that we discovered is that they have low levels of intrinsic Ca^{2+} buffering capacity. This creates a dependence upon on the endoplasmic reticulum (ER) to buffer Ca^{2+}. We found that ER release of Ca^{2+} through ryanodine receptors (RYRs) accompanied each spike, adding to the intracellular Ca^{2+} transient. These results show that ER Ca^{2+} induced Ca^{2+} release (CICR) is a significant feature of the physiology of LC neurons. CICR has been implicated in many forms of cellular plasticity and the response to stress.

In many neurons, spiking evoked Ca^{2+} entry increases cellular stress, particularly mitochondrial oxidant stress. To determine if this was the case in LC neurons, 2PLSM was used to monitor mitochondrial oxidant stress in *ex vivo* brain slices from transgenic mice expressing mito-roGFP under control of the cytomegalovirus promoter (*8*). These studies revealed that Ca^{2+} entry through L-type channels elevated mitochondrial oxidant stress in LC neurons. Increased spiking increased oxidant stress under normal conditions, suggesting that environmental stress that increased LC spiking would increase cellular oxidant stress. This mitochondrial oxidant stress was further shown to be dependent upon RYR release of Ca^{2+} from the ER and Ca^{2+} entry through the mitochondrial uniporter.

The activity-dependent elevation in mitochondrial oxidant stress was accompanied by an elevation in cellular levels of nitric oxide (NO). This was determined using 2PLSM and the nitric oxide sensor DAF-FM. NO production was attenuated by 1) antagonism of plasma membrane L-type calcium channels and 2) blocking the mitochondrial calcium uniporter. NO production was elevated by an antagonist of the mitochondrial sodium-calcium exchanger (NCX). These results are consistent with the hypothesis that mitochondrial Ca^{2+} entry stimulates a mitochondrial form of nitric oxide synthase (mtNOS) (*9*). NO produced by this mtNOS inhibits the electron transport chain (ETC) and increases the production of reactive oxygen species (ROS) (*10*), as two NOS inhibitors (L-NAME or L-NNA) significantly attenuated oxidation of mitochondrial matrix proteins in LC neurons.

The studies performed thus far show that basal and stress-driven activity increase oxidant stress in LC neurons. To determine whether this was subject to modulation, two manipulations were performed. LC neurons receive inhibitory GABAergic inputs during sleep, decreasing their activity and lowering wakefullness (*11*, *12*). To mimic this condition, LC neurons were inhibited by applying the $GABA_A$ receptor to *ex vivo* brain slices. This stopped pacemaking activity of LC neurons and dramatically decreased oxidant stress in LC neurons. To complement these studies, an arousing input was examined. LC neurons are innervated by neurons in the lateral hypothalamus (LH) that release orexin, leading to elevated LC neuronal activity in vivo (*13*, *14*). Bath application of orexin in *ex vivo* brain slices mimicked the effects *in vivo*. Surprisingly, orexin *decreased* oxidant stress in LC neurons. This was accomplished by diminishing the dependence of LC neurons on L-type Ca^{2+} channels during pacemaking. **These studies provided fundamental new insights into the mechanisms controlling the activity of LC neurons and how this activity causes cellular stress in conditions relevant to the battlefield.**

Activity-dependent release of NA by LC neurons is essential for the regulation of arousal and defensive behavior. However, very little is known about what controls the activity of LC neurons following the induction of PTSD. We have used fear conditioning

as a behavioral paradigm to begin to address potential adaptive changes in the intrinsic properties of LC neurons following PTSD induction. A cued fear-conditioning model has been used in our initial examination of this question (*15*). In this model, a mouse learns to associate a sound tone with an aversive stimulus. Specifically, three pairs of sound tones were paired with a electric shock; this led to freezing 24 and 48 hours later when mice were exposed to the sound tone alone (PTSD group). Another group of mice received three tones but no electric shock; they showed almost no freezing when presented with the sound tone 24 and 48 hours post-training (control group). After 48 hours of training, *ex vivo* brain slices were prepared; basal pacemaking activity in LC neurons was recorded in either whole cell or cell-attached configurations. *Preliminary findings from 5 mice per group (5 PTSD mice, and 5 control mice) suggest that tonic (pacemaking) spike rate is not altered in the PTSD group.* These studies were complemented by ones using 2PLSM imaging of dendritic Ca^{2+} oscillations during pacemaking. *As with the examination of spiking, dendritic Ca^{2+} oscillations were not significantly different in the PTSD group.*

Our next set of experiments will examine mice that have been conditioned using a physical restraint model (as proposed). We also will examine the effects of physiologically meaningful levels of CRH (release induced by cortisol) to determine if this affects LC neuron activity or oxidant stress. It could be that this input is lost during preparation of *ex vivo* brain slices.

Specific Aim 2: To characterize changes in the synaptic connections onto LC neurons from the cerebral cortex and amygdala in two mouse models of PTSD.

Previous studies have implicated afferent synaptic input from the cerebral cortex and amygdala as key to PTSD-induced adaptations in LC activity (*2*, *16-18*). However, it is not known how these synaptic inputs modulate the activity of LC neurons. To fill this gap, optogenetic approaches were used in a transgenic mouse expressing channelrhodopsin2 (ChR2) in cortical regions projecting to the LC (*11*). In *ex vivo* brain slices that allow rigorous characterization of synaptic properties, optogenetic activation of cortical axons reliably evoked glutamatergic synaptic responses in LC neurons. This was found using both full-field stimulation, as well as spot laser stimulation that allowed dendritic mapping of synaptic position. These studies revealed that cortical synapses were formed on both proximal and distal dendrites of LC neurons.

Next, transgenic mice were subjected to the fear-conditioning paradigm described above, allowing determination of whether these cortical inputs were affected. Brain slices were prepared 48 hours after training and cortical excitatory postsynaptic current (EPSCs) were evoked using whole-field photostimulation with blue light. *Our preliminary studies indicate that cortical synaptic responses in LC neurons are not altered by fear conditioning.*

The other synaptic input to LC neurons implicated in PTSD is from the amygdala. The central nucleus of the amygdala (CeM) it the principal projection to the LC (*19*, *20*). Two strategies are being developed to drive expression of ChR2 in CeM. One strategy uses intra-amgydalar injections of recombinant adeno-associated virus (rAAV) to express ChR2 specifically in the CeM subregion. This approach has been successfully applied. rAAV injection within the CeM region yielded ChR2 expression in axons reaching the LC and activation of these axons evoked EPSCs. Our second strategy (which is more labor intensive but should yield more consistent and complete ChR2 expression in neurons projecting to the LC) takes advantage of intersectional genomics and the fact that the amygdalar neurons projecting to the LC express corticotropin-releasing factor (CRF).

Specifically, transgenic mice expressing Cre-recombinase under control of the CRF promoter will be crossed with transgenic mice harboring a Cre-dependent ChR2 expression construct. These crosses should yield mice expressing Chr2 in all CRF expressing neurons. Another advantage of this approach is that neurons in the paraventricular nucleus of the hypothalamus (PVN) also express CRF (*12*, *16*); these neurons also project LC. CRF signaling has been demonstrated to play a role in stress-related anxiety disorders and therefore, adds another important tool to address potential adaptations of LC neurons and sensitivity to CRF signaling following fear conditioning. *Using these two approaches, we will test the hypothesis that fear conditioning leads to persistent alterations in the strength of amygdalar/PVN synaptic contacts on LC neurons.*

Specific Aim 3: To characterize the mechanisms governing the induction of long-term synaptic plasticity at cortical and amygdalar synapses onto LC neurons in two mouse models of PTSD.

Our effort during the last award period focused on Specific aims 1 and 2. Work on Specific aim 3 will begin in the next year.

4. KEY RESEARCH ACCOMPLISHMENTS:

- Autonomous spiking in LC neurons generated oscillations in somatodendritic Ca^{2+} concentration attributable to opening of L-type channels.
- Dendritic Ca^{2+} oscillations increased mitochondrial oxidant stress.
- By diminishing the reliance upon Ca^{2+} channels, orexin lowered mitochondrial stress while increasing pacemaking rate.
- The Ca^{2+}-dependent elevation in oxidant stress was dependent upon activation of a mitochondrial nitric oxide synthase.
- Antagonizing L-type channels lowers LC neuron stress
- Unaltered spike rate in LC neurons in the fear conditioning mouse model of PTSD
- Unaltered cortical glutamatergic input to LC neurons in the fear conditioning mouse model of PTSD

5. CONCLUSION:

In the first year of our program, we have made major progress toward our goals and made several discoveries that have important medical and military implications.

To date, our most important discoveries pertain to the mechanisms governing tonic activity and the resulting mitochondrial oxidant stress on LC neurons. These studies revealed that LC neurons utilize L-type Ca^{2+} channels to ensure that spiking continues during extended periods requiring vigilance and attention, like those encountered in battlefield conditions. This appears to be a feature that they share with other pacemaking neurons that provide essential neurological functions during periods of conflict, like dopaminergic neurons of the substantia nigra that speed movement. Although this design should create a survival advantage, it comes at the cost of elevated mitochondrial oxidant stress. While this does not pose a short-term problem, there could be significant negative long-term consequences of this stress, like impaired metabolism and cell senescence. These consequences could accelerate aging related decline in autonomic and cognitive control exerted by the LC. The identification of

dihydropyridines as modulators of this oxidant stress has obvious translational implications.

Because it is involved in the mechanisms underlying synaptic plasticity, intracellular Ca^{2+} oscillations accompanying normal activity could also be a major determinant of stress-induced changes in synaptic strength associated with PTSD.

Another key finding in the last year was that activity-dependent mitochondrial NO signaling is an important contributor oxidant stress. This provides an important conceptual advance and creates new therapeutic opportunities. This work also suggests that NO could play a role in LC adaptations to sustained or repeated stressors. Preclinical studies from other groups have suggested that NO plays an important role in the development of anxiety and PTSD (*21*) (*21*). NO is capable of modulating a wide range of cellular functions, including synaptic strength. In the next award period, we will examine the potential role of NO signaling in controlling the strength of cortical or amygdalar synapses.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

The work described characterizing the intrinsic calcium handling and mitochondrial oxidant stress dependent on nitric oxide signaling was submitted for publication to Nature Neuroscience in September 30th, 2013, and we received positive reviews in October 30th, 2013 and currently working in the revision of the manuscript for resubmission.

a. Publications:

Mitochondrial oxidant stress in locus ceruleus neurons is regulated by activity and nitric oxide synthase J. Sanchez-Padilla[1], J.N. Guzman[1], E. Ilijic[1], D.J. Galtieri[1], S. Schieber[3], W. Oertel[3], D. Wokosin[1], P. T. Schumacker[2], D. J. Surmeier[1] (in revision for Nature Neuroscience)

b. Presentations:

Functional Genomics Symposium, Tubingen, Germany – 4/12
State University of New York, Stony Brook – 4/12
17th International Parkinson's Disease Conference – 6/12
Brain Damage and Repair Meeting, Santander, Spain – 7/12
3rd World Parkinson's Disease Conference, Montreal, Canada – 9/12
Massachusetts Institute of Technology - 11/12

7. INVENTIONS, PATENTS AND LICENSES:

Nothing to report.

8. REPORTABLE OUTCOMES:

Nothing to report.

9. OTHER ACHIEVEMENTS:

Nothing to report.

10. REFERENCES:

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